Interleukin-10 and liver diseases

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Introduction

Cytokines are low-molecular weight proteins secreted by several cells which act through binding to membrane receptors in a hormone-like fashion. Lymphocytes and macrophages are the major sources of these mediators. A lot of other immune and non immune cells, including liver cells, also synthesise these peptides. Cytokines share several characteristics : they are pleiotropic and redundant messengers acting in an autocrine, paracrine and sometimes endocrine manner. Indeed, a single cytokine can have a wide range of biological effects in various cells and tissues and different cytokines may share similar properties. More recently, strong evidence was provided that cytokines attached to cell membranes (often called "pro-cytokines") play a major role in signal transmission to adjacent cells (juxtacrine signalling). Cytokines are grossly classified as pro- and anti-inflammatory. This does not mean that the formers are ugly and the latter's beneficial, it simply underlines the natural necessity to control defences and initiate a process of tissue repair after injury. Any rupture in the equilibrium between these mediators may lead to inappropriate inflammation and diseases. As opposed to tumour necrosis factor alpha (TNF-α) which is the prototype of pro-inflammatory cytokine involved in the development of several human diseases, interleukin-10 (IL-10), discovered in the late eighties, is a major anti-inflammatory cytokine.

Human IL-10 is a non glycosylated 18 kD peptide that becomes bioactive after dimerisation. Soluble IL-10 acts on a receptor which shares some intracellular signals with the interferon receptors. Membrane bound IL-10, like TNF, is also able to transduce signals, probably through a juxtacrine manner (1). Homologies between human and mouse IL-10 allow the use of the human protein in mice, but murine IL-10 is not active on human cells. Beside its potent anti-inflammatory and immunossupressive properties in vitro (Table 1) and in vivo (Table 2), IL-10 is also able to promote the recruitment, proliferation and cytotoxic activity of CD 8+ lymphocytes (2,3), to activate NK cells synergistically with IL-2 (4), to increase proliferation and immunoglobulin synthesis of B lymphocytes (5), type-1 Fc-γ receptor at the monocyte surface (6) and IL-15 production by monomacrophages (7). In some settings, the anti-inflammatory activity of endogenous IL-10 may preclude bacterial clearance by dampening important bactericidal activities (8,9) and by promoting B cell proliferation, it may also play a role in autoimmune disorders (10,11). This underlines the importance of considering all the efferent pathways of a cytokine before its introduction in the therapeutic armamentarium.

In 1992, we began to work on IL-10 in the context of liver diseases. At that time, tests to quantify the cytokine in biological samples, antibodies to block its activity or the recombinant protein were not commercially available. Therefore, the first results we obtained relied on generous gifts from the industry and a close collaboration with the Laboratory of Immunology in our institution. In the following years, several groups

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Table 1. — **In vitro anti-inflammatory and immunossupressive properties of IL-10**

Target cell	Stimulus	Effects	References
Monomacrophages	LPS	*Inhibition* of TNF, IL-1, IL-6, IL-8, IL-12, GM-CSF, Tissue Factor, arachidonic acid derivatives, nitric oxide, reactive oxygen intermediates *increases* IL-RA, sTNFR, MCP-1	(34,61,62)
Neutrophils	LPS	*Inhibition* of TNF, IL-1, IL-8 *increases* IL-1RA	(63,64)
Eosinophils	LPS	*Inhibition* of TNF, IL-8, GMCSF and cell survival	(65,66)
T cells + APC	Tcell stim	*inhibits* proliferation and IL-2 and IFN-γ	(62)
APC (monomacrophages, dendritic cells)	IFN-γ, Tcell stim	*Decreases* class II HLA, ICAM-1, B-7 cell surface expression	(62,67,68)
T cells	Tcell stim	*Inhibition* of IL-2, IL-5, *promotion* of anergy	(69,70)
Fibroblasts	IL-1 TNF	*inhibits* MCP-1, type-1 collagen *increases* sTNR, collagenase, stromelysin	(34,35)

including our laboratory have established that IL-10 is a key mediator in the liver, modulating the response to different injuries. The present review summarises the advances made in this area of investigation over the last five years.

The liver is a source of interleukin-10

An endogenous production of IL-10, resulting in increased serum levels was demonstrated in several experimental models of endotoxic shock or bacterial infections as well as in human sepsis (Table 2, (12)). Subsequently, blocking the natural release of IL-10 in this setting showed a dramatic increase of the inflammatory response and the mortality of animals, while treatment with exogenous IL-10 was able to significantly decrease the release of TNF and the consequent lethality (Table 2). At that time, it was thought that IL-10 was mainly produced by peripheral mononuclear cells. Since the liver is the richest organ in macrophages (Kupffer cells), it was postulated that the liver may represent an important source of IL-10 as it was already demonstrated for TNF (13). In fact, in 1993, Wagner *et al.* and Bischop *et al.* provided evidence that IL-10 messenger RNA was detectable in the liver of mice infected with Listeria monocytogenes and in human liver allografts during rejection, respectively (14,15). One year later, we showed that the liver was able to massively release the IL-10 protein during reperfusion of liver allografts by using simultaneous portal and hepatic vein sampling (16). Since then, several authors confirmed that the liver may be an important source of IL-10 in different experimental and human conditions (Table 3). As the liver is build with several cell types, a still ongoing challenge is to determine which kind of cell is mainly involved in IL-10 production during a specific stimulus. Presently, all but sinusoidal and biliary cells are able to disclose messenger RNA, immunohistochemical positivity or IL-10 protein release (Table 4). Kupffer cells are the best characterised cells involved in IL-10 and TNF synthesis, but the way they differentially regulate these cytokines is still unresolved and might depend on the initial stimulus. Indeed, gadolinium chloride, a Kupffer cell phenotype modifier, either inhibits or stimulates IL-10 production and has an opposite effect on TNF, if it is administered before partial hepatectomy or before lipopolysaccharide/galactosamine challenge, respectively (17-19). This might

Table 2. — **Anti-inflammatory activities of IL-10 in vivo which are not directly related to the liver**

Model	Species	Effects	References
Endotoxic shock (LPS)	mouse	Exogenous IL-10 : increased survival, decreased TNF Endogenous IL-10 : neutralisation increased mortality, TNF, IFN-γ, MIP2 and lung damage	(71,72)
Superantigen (SEB) and anti-CD3 induced shock	mouse	Endogenous IL-10 : neutralisation increased mortality and IFN-γ Exogenous IL-10 : increased survival, decreased cytokines	(73,74)
Septic peritonitis	mouse	Endogenous IL-10 : neutralisation increased mortality and TNF, however, TNF neutralisation did not increase survival.	(75)
Septic shock	humans	Ex vivo evidence that plasma IL-10 is a key mediator of monocyte deactivation during septic shock	(76)
Intravenous IL-10	humans	No adverse effects, decreased TNF and IL-1 production by ex-vivo LPS-stimulated PBMC, and decreased mitogen-induced T cell proliferation.	(54-56)
Delayed-Type Hypersensitivity (DTH)	mouse	Exogenous administration inhibits IL-2, IFN-γ, TNF and IL-6, vascular leakage and swelling	(77)
Enterocolitis	mouse	IL-10 knock-out mice spontaneously develop severe enterocolitis	(78)
Lung inflammation	mouse	Endogenous IL-10 is protective	(79,80)
Acute pancreatitis	mouse	Exogenous administration reduces necrosis, amylase/lipase levels and TNF mRNA expression	(81,82)

Table 3. — **Initial evidence that the liver is a source of IL-10**

Condition	Species	Year of publication	Reference
Listeria monocytogenes	Mouse	1993	(14)
Lipopolysaccharide	Mouse	1995	(83)
Lipopolysaccharide & propione bacterium acnes	Mouse	1995	(23)
Septic peritonitis	Mouse	1995	(84)
Tularemia	Mouse	1995	(85)
Pancreatitis	Mouse	1998	(20)
Autoimmune hepatitis and primary biliary cirrhosis	Humans	1994	(45)
Liver transplantation	Humans	1993	(15)
Ischaemia-reperfusion	Humans	1994	(16)
Liver cirrhosis	Humans	1996	(41,42)
Cardio-pulmonary bypass	Humans	1997	(86)

Table 4. — **Liver cells which disclose IL-10 RNA messenger and/or protein synthesis capability**

Cell	Species	Stimuli	Year of publication	Reference
Kupffer cells	Human	Lipopolysaccharide	1995	(87)
	Rat	Regeneration	1997	(17)
	Human	Lipopolysaccharide	1998	(88)
Hepatocytes	Mouse	TGF-b	1996	(89)
	Rat	Liver transplantation	1995	(90)
Stellate cells	Rat	Lipopolysaccharide, cytokines	1998	(33)
	Rat	Culture	1998	(36)
NK cells	Human	Interleukin-2	1998	(91)

also result from different cellular sources of IL-10 and TNF and/or gene transcription/translation differences. Nevertheless, it is now clear that several liver cells are able to synthesise IL-10, making this organ a major source of this anti-inflammatory cytokine. Beside the participation of the liver in the peripheral release of IL-10 in septic conditions, recent evidence was provided that in acute pancreatitis, the cytokine released by the liver is also able to control the systemic inflammatory process that may ultimately lead to multiple organ failure (20). In several experimental and human hepatic diseases IL-10 is also produced at the liver level (Table 3). In this setting, different stimuli are able to promote IL-10 production by liver cells, as polyclonal T-cell activators, endotoxins, reactive oxygen intermediates, viruses, parasites and bacteria. In fact, we clearly showed that reactive oxygen intermediates, are potent stimuli for IL-10 synthesis both by human monocytes (21) and by mouse livers subjected to cold ischaemia and reperfusion, as in the context of liver transplantation (22).

The role of endogenous interleukin-10

Considering the potent anti-inflammatory properties of IL-10 in experimental models of endotoxaemia where TNF plays a crucial detrimental effect, it was tempting to evaluate the effects of endogenously produced IL-10 in various experimental liver injuries. The first evidence that endogenous IL-10 could protect the liver came from Arai *et al.* in 1995 (23). They showed that dibutyryl cAMP was able to protect mice against liver injury induced by Corynebacterium acnes and LPS challenge. This beneficial effect was reported to be mediated through an increase in endogenous IL-10 production. In the same line of experiments, IL-10 knock-out mice were reported to succumb from severe liver necrosis when infected with Toxoplasma gondii while their control littermates did not (24). Subsequently, in three different models of experimental liver injury we provided evidence that endogenous IL-10 is able to control the release of pro-inflammatory cytokines both into the liver and in peripheral blood (19,25,26). Indeed, blocking IL-10 led to an increase in circulating or tissue TNF, IL-6, IFN-γ and IL-12 levels, and in liver necrosis depending on the initial stimulus (galactosamine/LPS, concanavalin A, carbon tetrachloride). Measurement of IL-10 tissue levels confirmed that it was produced within the liver (25) and that the suppression of endogenous IL-10 increased liver TNF content (27). However, these experiments, together with those from other laboratories, highlighted some peculiar properties of IL-10 in the liver. This cytokine is able to control liver inflammatory infiltrates and liver necrosis but also, and certainly with the same importance in a clinical point of view, liver regeneration and fibrosis. Indeed, a critical role for both TNF and IL-6 in liver regeneration was recently highlighted (28-30). In the partial hepatectomy rat model, blocking Kupffer cell IL-10 production with gadolinium chloride, increases TNF synthesis and liver regeneration compared to untreated animals (17). In the same way, we showed that IL-10 knock-out mice challenged with carbon tetrachloride are marginally affected in terms of liver necrosis, but disclose higher liver tissue TNF and hepatocyte staining for PCNA, a marker of cell proliferation (26). From these data it seems clear nowadays that IL-10 is able to control liver cell proliferation similarly to TGF-β (31), but with different kinetics (32). One year ago Wang *et al.* reported that hepatic stellate cells, which are mainly involved in liver fibrogenesis, are also able to release IL-10 upon different stimuli and exert an autocrine negative feed-back on collagen synthesis (33). Importantly, this anti-fibrotic property of IL-10, which was previously suggested in different experimental systems (34,35), disappears when cirrhosis develops. This property of hepatic stellate cells was recently confirmed (36), and its potential protective role in liver fibrogenesis simultaneously suggested in the study of Louis *et al.*, from our Laboratory and Thompson *et al.* (26,37). Both studies used chronic carbon tetrachloride injections in mice, a well known model of liver fibrogenesis. By repeatedly challenging IL-10 knock-out mice and their control littermates with carbon tetrachloride for at least 7 weeks, both authors showed that IL-10 deficient mice developed more liver fibrosis than wild type mice.

From these experimental studies, it can be currently concluded that endogenous IL-10 produced in the liver in various pathologic conditions is able to modulate inflammation, necrosis, cell proliferation and fibrosis.

Despite these experimental studies, we still do not know if such pathways are involved in human liver diseases. However, some recent tracks have to be followed. In North America and Europe, most of cirrhosis are related to alcohol consumption or virus C infection. It is clear that the human liver is able to synthesise IL-10 in different pathologic settings but it will never be possible to inhibit IL-10 production in this context due to evident ethical considerations. Therefore, only studies comparing IL-10 liver messenger RNA or IL-10 protein expression in a determined liver disease and in controls will be allowed.

A constant finding in patients with either stable alcoholic cirrhosis or with alcoholic hepatitis is their phenotypic TNF hypersecreting pattern observed after LPS stimulation of peripheral blood mononuclear cells (38-40). We hypothesised that this pattern could be due to defective IL-10 production by these cells. In fact, IL-10 release from LPS stimulated monocytes was clearly lower in alcoholic cirrhotic patients compared to controls (40). This was also suggested to occur at the liver level by IL-10 messenger RNA quantitative analysis (41). A comparable figure was found to occur during chronic hepatitis C and HCV related cirrhosis where liver IL-10 messenger RNA is decreased compared to patients devoid of liver disease, as is IL-10 release by peripheral mononuclear cells (42,43). Similarly, low IL-10 messenger RNA detected by in situ hybridisation and scanty IL-10 expression by immunochemistry is found in human liver biopsies during acute rejection of liver allografts (44). Together, these results suggest that a defective IL-10 production, which favours the release of pro-inflammatory cytokines, may occur in the context of some human liver diseases. On the opposite, an increased IL-10 production was reported in primary biliary cirrhosis and autoimmune hepatitis (45).

Interleukin-10 as a treatment in liver diseases

Since endogenous IL-10 controls several pro-inflammatory mediators in experimental liver injury and that some human liver diseases seem to be associated with low IL-10 production, it is tempting to speculate that the administration of exogenous IL-10 or the increase of its endogenous production could represent a new therapeutic challenge in liver diseases. In fact, numerous experimental studies have now provided evidence that the pharmacological use of IL-10 is able to protect the liver against several injuries. Together with Santucci *et al.*, we showed that pre-treatment of mice with IL-10 dramatically decreased TNF release, adhesion molecules expression, liver inflammatory infiltrates and liver injury after galactosamine and LPS challenge (19,46). Moreover, our study extended these observations to the therapeutic point of view since IL-10 treatment was still effective in protecting mice when the medication was administered 4 hours after the initiation of liver injury (19). In the model of concanavalin A induced hepatitis recently described by Tiegs *et al.* (47), liver infiltrating T cells, TNF and interferon-gamma play a major role in liver injury. In this setting, we showed

Table 5. — **Substances upregulating endogenous IL-10 production**

Compound	IL-10 source	References
IL-12	mouse non-T cells (in vivo)	(95,96)
IL-12 and IL-6	human T cells	(97)
TGF-β	mouse mesangial cells and macrophages (in vitro & in vivo)	(98,99)
IFN-α	human CD 4+ T cells and monocytes (in vitro)	(100,101)
IL-18	Mouse CD8+ T cells	(102)
GM-CSF	Human monocytic cell line	(103)
Cyclosporin-A	mouse non-T cells (in vivo)	(104)
Glucocorticoids	mouse macrophages (in vivo & in vitro), rat liver	(105-107)
PGE-2 and other cAMP elevating substances	mouse macrophages and human monocytes (in vitro & in vivo)	(23,93,108-111)
Chlorpromazine	mouse macrophages (in vivo)	(105,112)
L-N Monomethyl-arginine (NO synthase inhibitor)	mouse lymph node cells (ex vivo)	(113)
Desferrioxamine	mouse mesangial cells (in vitro)	(98)
Ebselen	Mouse after concanavalin A	(114)
Pyrrolidine dithiocarbamate (PDTC)	Mouse after lipopolysaccharide	(115)
SR 31747 (sigma ligand)	mouse macrophages (in vivo)	(116)
alpha-melanocyte stimulating hormone (α-MSH)	human monocytes (in vitro)	(117)
Adenosine and A3 agonists	Human monocytes, mouse after lipopolysaccharide	(21,118)
Gadolinium chloride	Mouse after galactosamine / lipopolysaccharide	(19)
Alcohol	Human monocytes	(119,120)
Linomide	Rats : autoimmune encephalomyelitis, human PBMC	(121,122)
Thalidomide analog	Mouse after lipopolysaccharide	(123)
Tyrphostin	Mouse autoimmune encephalomyelitis	(124)
Maxadilan (PACAP type 1 receptor agonist)	Mouse after lipopolysaccharide	(125)
Estrogens	Human CD4+ T cells	(126)
Ultraviolet B irradiation	Mouse lymph nodes	(127)
Urocanic acid	Mouse CD4+ T cells	(128)
Hind III liposomes	Double strand breaks in DNA, mouse epidermal cells	(129)
Dantrolene	Mouse after lipopolysaccharide	(130)
Histamine	Human PBMC	(131)

that exogenous IL-10 was able to dampen pro-inflammatory cytokines release as well as liver tissue damage (25). However, IL-10 is not always protective. In fact, after carbon tetrachloride challenge in mice, while decreasing TNF release, even high doses of exogenous IL-10 are not able to protect mice against free radical injury (H. Louis, personal communication, 1998). This does not mean that IL-10 is unable to control liver injury induced by reactive oxygen intermediates. Indeed, we recently reported that IL-10 either administered during reperfusion of cold preserved livers or before liver harvesting was able to dramatically decrease liver ischaemia-reperfusion injury (48), which is known to be associated with free radicals and pro-inflammatory cytokines production (49). Beside the control of inflammatory processes, exogenous IL-10 was also reported to act on other systems in the liver. This includes the decrease of foreign antigen presentation and expression of costimulatory molecules by liver sinusoidal endothelial and Kupffer cells (50,51). As far as cell proliferation or cell death is concerned, IL-10 is also able to limit hepatocyte proliferation (17,26) and promote apoptosis of monocytes or neutrophils (52,53).

To date, IL-10 was administered to healthy (54-56) or diseased humans in several trials. The drug is safe, without major side effect and is suggested beneficial in steroid resistant Crohn's disease, rheumatoid arthritis and psoriasis (57-59). However, beside the control of acute inflammatory burst, high doses of IL-10 when given to humans are also able to promote B cell activation with subsequent synthesis of antibodies which might preclude its use in some settings like kidney transplantation where it favours rejection in some patients (60). Aside of using the human recombinant protein, another therapeutic way would rely on increasing its endogenous production. As far as this therapeutic option is concerned, some old-fashioned medications are able to increase IL-10 production in vitro and in vivo, as do newly developed drugs targeting this property (Table 5).

Whether recombinant IL-10 or drugs enhancing its secretion will take place in the therapeutic armamentarium of liver diseases still needs a clear demonstration of the efficacy of the IL-10 protein in this setting and a comparison between the recombinant cytokine and the currently used or newly developed medications. Therefore, speculation and hope are the present and relevance might be the future.

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